Silver-Coated Nylon Dressing Plus Active DC Microcurrent for Healing of Autogenous Skin Donor Sites

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Introduction: Burn wounds are a significant cause of morbidity and mortality, and improved outcomes are demonstrated with early closure of both primary burn wounds and skin donor sites. Thus, technology that decreases the healing time of burns and donor sites would be potentially lifesaving. We present the results of a single-center, prospective, double-blinded, randomized controlled trial to evaluate the efficacy of silver-coated dressing with active microcurrent in comparison to silver-coated dressing with sham microcurrent on wound-closure time for autogenous skin donor sites.

Methods: Four hundred five patients were screened for treatment of their donor sites using a silver-coated nylon dressing with either sham or active microcurrent stimulation. Thirty patients were enrolled in the study and then randomized. Of these, 5 patients were removed from analysis due to protocol deviations. Differences in time-to-closure were analyzed using Kaplan-Meier analysis and the proportional hazard regression model. Subjective verbal pain rating scores (0–10; 0, no pain; 10, worst pain) were also recorded. All devices were blinded and programmed at an outside facility, so that every patient had either an active or sham device. The study was unblinded only after the final patient's donor site had healed. All patients achieved donor-site healing before postoperative day 20. The 14 patients in the active microcurrent group [mean, 10.8 (2.9) days; range, 7–15 days] experienced no difference in time to wound healing as compared to the remaining patients in the sham microcurrent group [mean, 11.1 (2.0) days; range, 8–14 days; $P = 0.75$]. There were no differences in pain from one group compared to the other. None of the donor sites exhibited clinical signs of infection.

Conclusions: In a sample size of 25 burn patients, the addition of direct microcurrent to silver-nylon dressings did not decrease time to wound closure of skin donor sites, and it did not show a difference in reported pain levels.

Key Words: burns, electric stimulation therapy, silver, bandages, skin transplantation, wound healing

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Patients with burn injuries have improved outcomes with earlier closure of their wounds.[1] Donor-site healing is often the rate-limiting step in wound closure for those patients who require multiple skin-grafting operations. For these patients, interventions that decrease donor-site healing time would be potentially lifesaving; for less severely injured patients, such interventions would reduce hospital length of stay.

The impact of microcurrent on wound healing was evaluated by Chu et al in a series of small animal studies at this center. Rats sustained 20% total body surface area (TBSA) full-thickness scald burns, and the burns were inoculated with *Pseudomonas aeruginosa*. The effects of silver-nylon dressing and direct microcurrent, applied continuously for 5 days, were then evaluated. Used as a surface anode with an implanted silver needle cathode, the device significantly improved wound healing time, at currents between 0.4 and 10 μA. These results were not reproduced when the silver-nylon dressing was used as a surface cathode. There was no difference in survival time between the silver-nylon-and-microcurrent-treated group and a group treated with silver sulfadiazine cream for 10 days.[2] Another study in the rat model evaluated the effect of DC on edema formation. Microcurrent, but not silver nylon alone, reduced burn wound edema by approximately 17% to 48% when applied at different times up to 48 hours postburn.[3] This effect was confirmed by studies of Evans blue dye accumulation.[4] DC current accelerated the healing of tangentially excised deep partial thickness burn wounds in guinea pigs (2 vs 7 days for complete revascularization).[5] Taken together, these studies indicated that DC microcurrent exerted both anti-infective and prohealing effects in the small animal models.

Despite this body of work, only 2 studies of DC microcurrent in human burn patients have been published. Huckfeldt and colleagues[6] reported that DC current, applied to silver-nylon-dressed skin-graft sites, caused a 36% reduction in time to wound closure. More recently, Blount and colleagues[7] reported that a bioelectric dressing (which does not require an external power source), applied to donor sites, resulted in a similar acceleration in wound healing.

We conducted a single-center, prospective, double-blinded, randomized controlled trial to evaluate the efficacy of silver-nylon dressings with active microcurrent, in comparison to silver-nylon dressings with sham microcurrent, for reducing the healing time of autogenous skin donor sites in burn patients. We hypothesized that DC microcurrent would result in faster donor-site wound healing.

METHODS

This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board, and in accordance with the approved protocol.

Study Design

Thirty burn patients were randomized for treatment of split-thickness skin donor sites using either a silver-nylon dressing with active microcurrent device (study group), or a silver-nylon dressing with sham microcurrent device (control group). A single donor site was studied in each enrolled patient. The primary end point was time to 90% confluent reepitheliazation of the donor site, as judged by an investigator. The secondary end points included pain and infection (see later). Patients who met the inclusion criteria for this study listed below were consented, enrolled, and scheduled for burn excision. The inclusion criteria were as follows: (a) patient was between 18 and 65 years, of either sex, and in good general health before injury; (b) burn wounds of less than 30% TBSA; (c) burn wounds did not involve the donor-site harvest areas; (d) patient required excision and grafting of sufficient extent to justify a donor site on a nondependent body surface; (e) patient agreed to participate in follow-up evaluation.

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The exclusion criteria were as follows: (a) burn size greater than 30% TBSA; (b) donor site had been previously harvested; (c) bloodstream infection, burn-wound infection, hemodynamic instability requiring the use of pressors, or critical illness such as one requiring preoperative ventilator support; (d) diabetes, peripheral vascular disease, cirrhosis, or renal failure; (e) patient received medications that inhibit/compromise wound healing (eg, therapeutic-dose anticoagulants, antiplatelet drugs, or corticosteroids); (f) implanted pacemaker; (g) pregnancy or nursing; (h) sensitivity to silver or nylon; and (i) patient unable to provide written informed consent.

Study Device

The active microstimulator device was a battery-operated, portable, 900-mV generator configured to produce a series of signals (15–50 μA) that were repeated continuously. The variable current is scheduled to accommodate variance in the wound bed resistance. The current generated is below the perceptible level of 1 mA, at which individuals experience a slight tingling sensation. All devices, active and sham, were identical in appearance. They were blinded and programmed at an outside facility, so that every patient had either an active or sham device. The study was unblinded only after the final patient's donor site had healed.

Surgical Procedures

In the operating room, excision and grafting of the burn wounds was conducted in the usual fashion. For harvesting of the subject's donor sites, a Zimmer dermatome with a 4-in guard was used by the principal investigator, co-investigators, or other burn surgeon staff to harvest sites at 10/1000th of an inch (0.254 mm) in depth of uniform size. A donor site that was approximately 11 × 11 cm in size or greater and located on the anterior or lateral surfaces of the body that had not been previously harvested was identified for study. Moistened silver-nylon dressings were applied directly to the wounds. The black conductive surface of a TENS electrode was placed in the middle of the silver-nylon dressing and a wire connected the electrode to the study device. The entire dressing was covered by coarse mesh gauze. The circuit was completed with a second wire attached to a grounding pad at a distant, uninjured site. The system became automatically activated (in the active group ONLY) once the electrodes were connected.

Postoperative Care

The gauze dressings were remoistened with sterile water up to 4 times daily. If the patient was in bed, the device could be placed near the bedside. If patients ambulated, then ace wraps were used to protect the system. The gauze dressing and Ace bandages were changed on postoperative day 1, and daily thereafter until healing occurred. The electrodes were examined and replaced if the conductive gel dried out. After applying a new gauze dressing, the connection between the electrode and the stimulator unit was checked. The grounding electrode was also examined to insure good skin contact, and these electrodes were replaced when necessary. The edges of the donor site were inspected for evidence of healing or infection on postoperative day 3. The silver-nylon dressing was removed and replaced (if needed). The donor site was completely exposed and inspected on postoperative day 4. The silver-nylon dressing was then rinsed with sterile water daily and changed as needed until the wound was healed. In the event that the dressing could not be rinsed, a new silver-nylon dressing was placed over the donor site.

The wound was defined as having healed when 90% or more of wound surface was confluently reepithelialized (and an investigator judged that the donor site would be suitable for reharvesting). Photographs and subsequent expert evaluation blinded to the study group evaluated the wounds for healing. Standardized digital photographs were used to document wound healing time. Secondary end points of pain (assessed using a Verbal Rating Scale of 0–10; 0, no pain; 10, worst pain) and infection were monitored daily using surgeon's assessments and case report forms. Agreed upon signs and symptoms of potential infection included increased pain, redness, swelling, purulent discharge, temperature, and lack of healing improvement. (Microbiological studies of donor sites were not performed, as the method of diagnosis of donor-site infection used at this burn center is clinical rather than microbiological.) Exploratory analysis was conducted to assess inflammation, pain medication (type, dosage, route, and timing), and care required for wound management (rinsing and replacement sheets as described previously).

After Discharge

At discharge, the patient and/or caregiver were given written instructions and hands-on training on how to take care of the dressing and microcurrent stimulator. The patients were instructed to charge the battery for 30 minutes daily, by plugging the charger cord into the microcurrent stimulator. A research nurse monitored patient compliance by recording the amount of time the microcurrent stimulator was disconnected. Patients were instructed to return to the hospital for donor-site assessment on postoperative day 4. The burn surgeon determined the timing of any subsequent visits based on the condition of the wound on day 4. Follow-up occurred on days 6, 8, 10, and so forth. In the event the patient did not return for any of the scheduled assessments, a research nurse called the patient to screen the donor-site's condition. The patient was then asked to return to the hospital for the next scheduled assessment. If the donor site was healed, the patient was asked to return to the hospital for an evaluation and/or photographs. If the day of healing was missed and no photographs were taken, the patient was asked to return the following day for pictures and evaluation. In the event that visualization of the donor site by the research team was not conducted, the patient was withdrawn from the study.

Data Analysis

nQuery Advisor 4.0 software was used to determine the sample size necessary to achieve 80% power to detect a difference in healing time of 2 days with a common standard deviation (SD) of 1.83 and a 2-sided $\alpha = 0.05$. The SD was obtained from the study of Huckfeldt et al.[6] A difference of 2.0 days was considered to be both clinically and statistically significant. Microsoft Excel was used to collect and manage data under a password-protected file. The data were screened for accuracy and normality assumptions before analysis. Data analysis was performed by a statistician who was blinded to the treatment assignment. Time to wound closure was compared between the 2 groups with Kaplan-Meier analysis and the proportional hazard regression model. Exploratory assessments evaluated patient's perception of pain as measured on a Verbal Rating Scale between the 2 groups. The presence of infection at the donor site between the 2 groups was tracked, although none was identified. Data are reported as means (SD), unless otherwise noted. Statistical significance was accepted at $P < 0.05$.

RESULTS

Four hundred five patients were screened for inclusion in the study. Thirty patients were enrolled in the study. Of these, 5 patients were removed from analysis due to protocol deviations. One patient initially qualified based on inclusion criteria, but later developed pneumonia and septic shock. Three patients did not comply with the follow-up requirements. In the fifth case, the patient disconnected the microcurrent device for more than 24 hours. Of the remaining 25 patients, 2 were female and 23 were male; 11 were military personnel (currently on active duty) and 14 nonmilitary. Their ages ranged from 22 to 55 years [mean, 33.8 (9.5) years]. All had burns of less than 20% of the percentage of TBSA [mean, 6.6% (4.7%)].

All patients achieved donor-site healing before postoperative day 20. Ineffective or failed healing was not observed in this study; nor

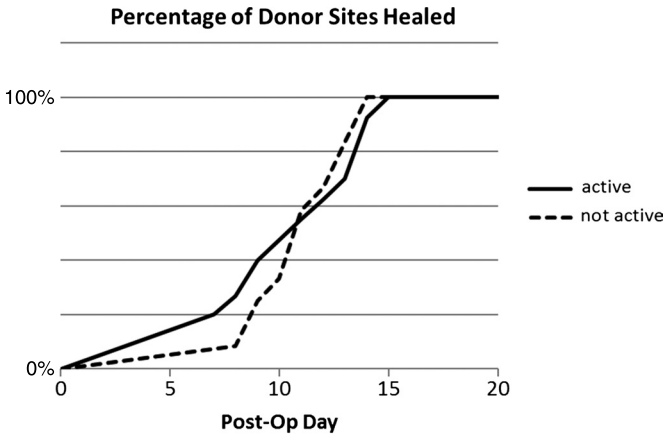

FIGURE 1. Number of donor sites healed as a function of postoperative day.

was donor-site cellulitis. The 14 patients in the active microcurrent group [mean, 10.8 (2.9) days; range, 7–15 days] experienced no difference in time to wound healing compared to the patients in the sham microcurrent group [mean, 11.1 (2.0) days; range, 8–14 days; $P = 0.75$]. A trend appeared in which more patients in the active microcurrent group healed before day 10 (see Fig. 1), but this observation was not statistically significant.

The Verbal Rating Scale (0–10) for pain was evaluated. In an analysis of changes in pain rating over time, the patients reported a decreased perception of pain with a later postoperative day ($P < 0.001$) (Fig. 2). The maximum level of pain, on average, occurred on postoperative day 2 at 2.7 (2.7). However, when comparing the active and sham groups, there was no difference in pain reported ($P = 0.46$). No donor-site infections were identified. No complications related to the use of DC microcurrent were observed.

DISCUSSION

The principal finding in this study was that the addition of DC microcurrent to a silver-nylon dressing was not associated with a decrease in donor-site healing time in burn patients. This discussion will focus on the effects of silver on wound healing, and the effects of microcurrent on wound healing.

Because of the widespread use of silver dressings for the treatment of thermal injuries and other wounds, several studies have evaluated silver dressings for their effect on wound healing. Olson et al evaluated 72 donor-site wounds in 6 pigs. Xeroform gauze was compared to Acticoat dressings (Smith & Nephew); the latter is a nanocrystalline silver dressing. Reepithelialization occurred in 7 days for Acticoat versus 10 days for Xeroform.[8] Innes et al[9] compared 16 paired donor sites on 15 patients, treated with Allevyn versus Acticoat. Allevyn (Smith & Nephew) is a trilaminar hydrophilic polyurethane dressing. Allevyn healed faster (9.1 vs 14.5 days). By contrast, Argirova et al studied 27 burn patients. Fifteen donor sites were treated with Acticoat, and 12 donor sites with Allevyn. There was faster epithelialization by 1.7 days and decreased pain with Acticoat.[10] Demling and DeSanti compared Acticoat and Xeroform gauze (the latter moistened with neomycin/polymixin) for treatment of 2:1 meshed skin grafts in 20 patients. The day of healing was 7 for Acticoat and 10 for Xeroform.[11]

Taken together, a plausible mechanism for the differences achieved in these studies is the value of moist wound healing. Could there be other mechanisms specific to silver? In a porcine model of contact dermatitis induced by 1,2-dinitrochlorobenzene, Nadworny et al demonstrated that Acticoat induced apoptosis of inflammatory cells in the dermis, along with decreased levels of the proinflammatory cytokines TNF-α and IL-8, increased levels of the anti-inflammatory cytokine IL-4, and increased levels of epidermal growth factor, keratinocyte growth factor (KGF), and KGF-2. These authors claim that the effects are unique to nanocrystalline silver, in that 0.5% silver nitrate induced more widespread apoptosis.[12,13] Other studies indicate that silver may be toxic to fibroblasts and keratinocytes.[14] Thus, the overall effect of silver dressings on wound healing is uncertain.

More important for our study is the mechanism of action of microcurrent. Levin and Stevenson reviewed regulation of cell behavior and tissue patterning by endogenous bioelectric signals. Transmembrane voltage provides signals that regulate cell behavior during both embryonic development and regenerative repair. It is an important regulator of proliferation, migration, differentiation, and apoptosis.[15] McCaig and colleagues noted that injury causes an immediate voltage gradient, with the center of the wound positively charged. This means that "cell behaviors within ~500 μm of a wound edge in skin and cornea…take place within a standing gradient of voltage." As the distance from the wound increases, the voltage (and its effects on cells) drops exponentially. Then, with healing, the voltage gradient disappears. The authors suggest that "both single cells and sheets of cells may use electrical strategies in mounting a wound-healing response…in evolutionary terms, membrane resealing to close an electrical leak is among the most primitive activities that cells undertake."[16]

Can these endogenous phenomena be harnessed by externally applied fields? Funk and Monsees reviewed the molecular basis for the effects of externally applied electromagnetic fields on cells. Over the last decade, much work has been done to try to determine how such fields, applied to the cell membrane, may influence the "classic" biochemical pathways inside the cell; this picture remains incomplete.[17,18] Despite this gap, externally applied fields have been used in wound-healing studies for more than 30 years.

A common use of electromagnetic field therapy is in the treatment of fractures. For example, Webster et al applied DC current to the wounds of 25 patients with chronic, actively draining osteomyelitis. They had all experienced failure of conventional treatment such as debridement and antibiotics. Sixteen patients healed; there were no controls.[19] Later, the effects of a pulsed electromagnetic field (PEMF) on late bone healing phases using an osteotomy gap model in the canine mid-tibia were investigated. PEMF stimulation provided faster recovery of load-bearing, an increase in new bone formation, and higher mechanical strength.[20] Despite these and other encouraging preclinical studies, a Cochrane review of 4 randomized clinical trials (125 patients) found insufficient evidence on the efficacy of electromagnetic field therapy on delayed union or nonunion of fractures.[21]

Other studies have addressed the role of microcurrent in the healing of burn wounds or donor sites. In a porcine model of 0.3-mm

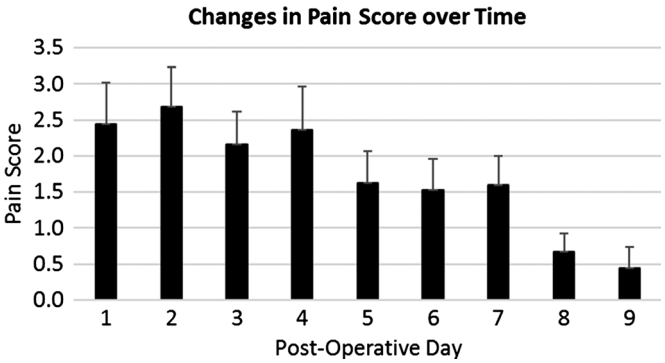

FIGURE 2. Verbal Rating Scale for Pain as a function of postoperative day for all patients. [$P < 0.001$ for changes over time. Data are means (SEM).]

excisional wounds, DC (50–300 μA) led to an increase in collagen synthetic capacity on days 5 to 7, attributed to an augmentation of the number of collagen-producing cells. This increased number of cells could be due to proliferation or to chemoattraction into the wound. Also, there was an increase in wound epithelialization with DC.[22]

As previously mentioned, extensive preclinical studies by Chu and colleagues demonstrated that DC microcurrent, applied to a silver-nylon dressing, exerted several beneficial effects on wound healing. These included improved survival following burn-wound infection, and more rapid healing of skin donor sites and of excised and grafted burn wounds.[2,3,5,23] The beneficial effect on edema formation was documented by other researchers in a rat hindlimb model. Microcurrent stimulated the movement of blue-dye–labeled albumin into the lymphatic vessels, increasing oncotic pressure and drawing fluid into the vessels. Distention of the lymphatic vessel lumen increased vessel contraction, and thus reduced inflammation in the limb.[24] Microcurrent also may reduce wound healing time by increasing ATP production, protein synthesis, and membrane transport. For example, an in vitro study using rat skin found that microcurrent increased ATP production up to 400%, glycine incorporation into skin proteins up to 75%, and aminoisobutyric acid uptake through the cell membrane by 30% to 40%.[25]

Our study has several limitations. We chose to use a direct current ranging from 10 to 50 μA. A potential limitation to the study design lies with the delivery of the microcurrent. The devices were designed to report breaks in the scheduled current delivery. The active microcurrent devices were programmed to deliver a current that varied based on the wound bed's resistance. Each of the devices was tested before being applied to the patients and upon wound healing. The system design did not permit us to measure the actual electrical delivery while the device was attached to the patient. Furthermore, we did not measure the electric field inherent in the wound[26] with the silver dressing in place and before application of external current. Whether the application of a silver dressing alone has a local electrical effect is unknown. However, a novel bioelectric dressing, incorporating zinc and silver microcells to generate local current without the need for an external generator, accelerated donor-site healing in a recent study.[7]

We used a study design in which patients were randomized to one treatment or the other. An alternate study design would have used 2 donor sites in each patient, with donor sites randomized to one treatment or the other. With the study design used, we cannot exclude the influence of unmeasured interpatient factors on the outcome. Our inclusion criteria were established to minimize the effects of confounding factors. More than 400 patients were screened to enable the enrolment of 30 individuals who met the inclusion criteria and were willing to consent to the follow-up requirements and other rules of the study. This experience indicates the difficulty inherent in conducting research in the thermally injured population, which frequently presents with comorbid conditions. We found that patients required reminders to conduct daily recharges of the stimulator. So, a comparable dressing with fewer management requirements would be advantageous.

In conclusion, extensive preclinical studies and small clinical studies indicate the potential use of DC microcurrent in the healing of donor sites and burn wounds. We did not identify a therapeutic effect of DC microcurrent in addition to silver-nylon dressings in the present study of donor-site healing. More work is needed to develop approaches to accelerate donor-site healing in burn patients, especially those which could be extrapolated to the critically ill burn patient where fast donor-site healing time is so essential.

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